Exhaled Nitric Oxide Measurement

File Name: exhaled_nitric_oxide_measurement
Origination: 2/2009
Last CAP Review: 3/2018
Next CAP Review: 3/2019
Last Review: 3/2018

Description of Procedure or Service

Asthma is characterized by airway inflammation that leads to airway obstruction and hyperresponsiveness, which in turn lead to characteristic clinical symptoms including wheezing, shortness of breath, cough, and chest tightness. Guidelines for the management of persistent asthma stress the importance of long-term suppression of inflammation using steroids, leukotriene inhibitors, or other anti-inflammatory drugs. Existing techniques for monitoring the status of underlying inflammation have focused on bronchoscopy, with lavage and biopsy, or analysis by induced sputum. Given the cumbersome nature of these techniques, the ongoing assessment of asthma focuses not on the status of the underlying chronic inflammation, but rather on regular assessments of respiratory parameters such as FEV1 and peak flow. Therefore, there has been interest in noninvasive techniques to assess the underlying pathogenic chronic inflammation as reflected by measurements of inflammatory mediators.

Management

Guidelines for the management of persistent asthma stress the importance of long-term suppression of inflammation using steroids, leukotriene inhibitors, or other anti-inflammatory drugs. Existing techniques for monitoring the status of underlying inflammation have focused on bronchoscopy, with lavage and biopsy, or analysis by induced sputum. Given the cumbersome nature of these techniques, the ongoing assessment of asthma focuses not on the status of the underlying chronic inflammation, but rather on regular assessments of respiratory parameters such as forced expiratory volume in 1 second and peak flow. Therefore, there has been interest in noninvasive techniques to assess the underlying pathogenic chronic inflammation as reflected by measurements of inflammatory mediators.

Fractional Exhaled Nitric Oxide and Exhaled Breath Condensate

Two proposed strategies are the measurement of exhaled nitric oxide and the evaluation of exhaled breath condensate. Nitric oxide is an important endogenous messenger and inflammatory mediator that is widespread in the human body, functioning, for example, to regulate peripheral blood flow, platelet function, immune reactions, and neurotransmission and to mediate inflammation. While the role of NO in asthma pathogenesis is still under investigation, patients with asthma have been found to have high levels of exhaled NO, which decreases with treatment with corticosteroids. In biologic tissues, nitric oxide is unstable, limiting measurement. However, in the gas phase, nitric oxide is fairly stable, permitting its measurement in exhaled air. Exhaled nitric oxide is typically measured during single breath exhalations. First, the subject inspires nitric oxide-free air via a mouthpiece until total lung capacity is achieved, followed immediately by exhalation through the mouthpiece into the measuring device. Several devices measuring exhaled NO are commercially available in the United States. According to a 2009 joint statement by the American Thoracic Society and European Respiratory Society, there is a consensus that the fractional concentration of exhaled nitric oxide (FeNO) is best measured at an exhaled rate of 50 mL per second (FeNO 50 mL/s) maintained within 10% for more than 6 seconds at an oral pressure between 5 and 20 cm H2O. (1) Results are expressed as the nitric oxide concentration in parts per billion (ppb), based on the mean of 2 or 3 values.
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Exhaled breath condensate (EBC) consists of exhaled air passed through a condensing or cooling apparatus, resulting in an accumulation of fluid. Although EBC is primarily derived from water vapor, it also contains aerosol particles or respiratory fluid droplets, which in turn contain various nonvolatile inflammatory mediators, such as cytokines, leukotrienes, oxidants, antioxidants, and various other markers of oxidative stress. There are a variety of laboratory techniques to measure the components of EBC, including such simple techniques as pH measurement, to the more sophisticated gas chromatography/mass spectrometry or high performance liquid chromatography, depending on the component of interest.

**Clinical Uses of FeNO and EBC**

Measurements of FeNO have particularly been associated with an eosinophilic asthma phenotype. Eosinophilic asthma is a subtype of severe asthma associated with sputum and serum eosinophilia, along with later-onset asthma. Until recently, most asthma management strategies did not depend on the recognition or diagnosis of a particular subtype. However, 2 anti-interleukin 5 inhibitors have been approved by the Food and Drug Administration (FDA) for the treatment of severe asthma with an eosinophilic phenotype. An anti-interleukin 4 and 13 monoclonal antibody has also been shown to improve uncontrolled asthma, with the greatest improvement observed in the subgroup of patients with the highest blood eosinophil count.

Measurement of nitric oxide and EBC has been investigated in the diagnosis and management of asthma. Potential uses in management of asthma include assessing response to anti-inflammatory treatment, monitoring compliance with treatment, and predicting exacerbations. Aside from asthma, they have also been proposed in the management of patients with chronic obstructive pulmonary disease, cystic fibrosis, allergic rhinitis, pulmonary hypertension, and primary ciliary dyskinesia.

**Regulatory Status**

In 2003, the U.S. Food and Drug Administration (FDA) cleared for marketing the Nitric Oxide Monitoring System (NIOX®) (Aerocrine; Sweden) with the following indication: “[Measurements of the fractional nitric oxide (NO) concentration in expired breath (FE-NO)] provide the physician with means of evaluating an asthma patient's response to anti-inflammatory therapy, as an adjunct to established clinical and laboratory assessments in asthma. NIOX should only be used by trained physicians, nurses and laboratory technicians. NIOX cannot be used with infants or by children approximately under the age of 4, as measurement requires patient cooperation. NIOX should not be used in critical care, emergency care or in anesthesiology."

In March 2008, the NIOX MINO was cleared for marketing. The main differences between this new device and the NIOX are that the NIOX MINO is hand-held and portable and that it is not suitable for children under age 7 years. In November 2014, the NIOX VERO, which differs from prior devices in terms of its battery and display format was cleared for marketing by the FDA.

The RTube™ Exhaled Breath Condensate collection system (Respiratory Research, Inc) and the ECoScreen EBC collection system (CareFusion, Germany) are registered with the FDA as a Class I device that collects expired gas. Respiratory Research has a proprietary gas-standardized pH assay, which, when performed by the company, is considered a laboratory-developed test.

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

**Policy**

Measurement of exhaled or nasal nitric oxide or exhaled breath condensate is considered investigational for the diagnosis and management of asthma and other respiratory disorders. BCBSNC does not provide coverage for investigational services or procedures.
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Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Exhaled Nitric Oxide Measurement is covered

Not applicable.

When Exhaled Nitric Oxide Measurement is not covered

Measurement of exhaled or nasal nitric oxide is considered investigational in the diagnosis and management of asthma and other respiratory disorders including but not limited to chronic obstructive pulmonary disease and chronic cough.

Measurement of exhaled breath condensate is considered investigational in the diagnosis and management of asthma and other respiratory disorders including but not limited to chronic obstructive pulmonary disease and chronic cough.

Policy Guidelines

Evaluation of exhaled nitric oxide and exhaled breath condensate (EBC) are proposed as techniques to diagnose and monitor asthma and other respiratory conditions. There are commercially available devices for measuring NO in expired breath and various laboratory techniques for evaluating components of EBC.

For individuals who have suspected asthma who receive measurement of fractional exhaled nitric oxide (FeNO), the evidence includes multiple retrospective and prospective studies of diagnostic accuracy, along with systematic reviews of those studies. Relevant outcomes are test accuracy and validity, symptoms, change in disease status, morbid events, and functional outcomes. There are multiple reports on the sensitivity and specificity of FeNO in asthma diagnosis; however most studies are in the setting of patients with asthma symptoms without previous testing. The available evidence is limited by the use of wide variability in FeNO cutoff levels used to diagnose asthma, and lack of data on performance characteristics in diagnostic challenging settings. The accuracy of the cutoffs recommended by the American Thoracic Society guidelines has not been evaluated in the diagnosis of asthma. In addition, no studies were identified that evaluated whether use of FeNO improved the accuracy of asthma diagnosis compared with clinical diagnosis. For use of FeNO in the diagnosis of eosinophilic asthma, using the criterion standard of sputum eosinophilia, the diagnostic accuracy is moderate. The evidence is insufficient to determine the effect of the technology on health outcomes.

For individuals who have asthma and who receive medication management directed by FeNO, the evidence includes diagnostic accuracy studies, multiple randomized controlled trials (RCTs) and systemic reviews of those trials. Relevant outcomes are symptoms, change in disease status, morbid events, and functional outcomes. The available RCTs evaluating the use of FeNO tests for the management of patients have not consistently found improvement in health outcomes. Two Cochrane reviews from 2016, one on adults and the other on children, found FeNO-guided asthma management reduced the number of individuals who had more than 1 exacerbation, but had no impact on day-to-day symptoms. The evidence is insufficient to determine the effect of the technology on health outcomes.

For individuals who have suspected or confirmed respiratory disorders other than asthma who receive measurement of measurement of FeNO, the evidence includes 1 crossover trial and observational studies. Relevant outcomes are test accuracy and validity, symptoms, change in disease status, morbid
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events, and functional outcomes. The available evidence for the use of FeNO for respiratory disorders other than asthma is limited by heterogeneity in the conditions evaluated and uncertainty about how the test fits in defined clinical management pathways. The evidence is insufficient to determine the effect of the technology on health outcomes.

For individuals who have suspected or confirmed respiratory disorders who receive measurement of exhaled breath condensate (EBC), the evidence includes observational studies reporting on the association between various EBC components and disease severity. Relevant outcomes are test accuracy and validity, symptoms, change in disease status, morbid events, and functional outcomes. There is considerable variability in the particular EBC components measured and criteria for standardized measurements. The evidence is insufficient to determine the effect of the technology on health outcomes.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable codes: 83987, 94799, 95012

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

BCBSA TEC Assessment [Electronic Version]. February 2006


Specialty Matched Consultant Advisory Panel review meeting 3/30/11

Specialty Matched Consultant Advisory Panel review 3/2012


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BCBSA Medical Policy Reference Manual [Electronic Version]. 2.01.61, 9/14/17

Specialty Matched Consultant Advisory Panel 3/2018

Medical Director review 3/2018

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.01.61, 6/14/18

Policy Implementation/Update Information

<table>
<thead>
<tr>
<th>Date</th>
<th>Description</th>
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<tbody>
<tr>
<td>3/2/09</td>
<td>New policy issued. Measurement of exhaled or nasal nitric oxide, or collection and analysis of exhaled breath condensate, is considered investigational in the diagnosis and management of asthma and other respiratory disorders. (adn)</td>
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<tr>
<td>1/5/10</td>
<td>CPT Code 0140T deleted and replaced with CPT 83987.</td>
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<tr>
<td>6/22/10</td>
<td>Policy Number(s) removed (amw)</td>
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<tr>
<td>2/15/11</td>
<td>CPT Code 0064T deleted from Billing/Coding section. (adn)</td>
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<tr>
<td>4/12/11</td>
<td>Description and Policy Guidelines sections extensively revised. Not Covered section changed to read: “Measurement of exhaled or nasal nitric oxide is considered investigational in the diagnosis and management of asthma and other respiratory disorders including but not limited to chronic obstructive pulmonary disease and chronic cough. Measurement of exhaled breath condensate is considered investigational in the diagnosis and management of asthma and other respiratory disorders including but not limited to chronic obstructive pulmonary disease and chronic cough.” Specialty Matched Consultant Advisory Panel review meeting 3/30/11.</td>
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<tr>
<td>3/30/12</td>
<td>Specialty Matched Consultant Advisory Panel review 3/2012. Added references and updated policy guidelines. No change to policy statement. (lpr)</td>
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<td>4/16/13</td>
<td>Specialty Matched Consultant Advisory Panel review meeting 3/20/13. Reference added. No change to policy statement. (lpr)</td>
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<tr>
<td>2/25/14</td>
<td>Description and Policy Guidelines sections updated. References updated. No change to policy statement. (lpr)</td>
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5/13/14  Specialty Matched Consultant advisory panel review meeting 4/30/2014. No change to policy statement. (lpr)

4/28/15  Updated the “Description and Policy Guidelines” sections. Reference added. Specialty matched consultant advisory panel review 3/25/2015. No change to policy statement. (lpr)


7/26/16  Updated Policy Guidelines section, Reference added. No change to policy statement. (lpr)


10/13/17 Added CPT 94799 to Billing/Coding section. Updated Description and Policy Guidelines sections. No change to policy statement. Reference added. (lpr)

4/27/18  Specialty Matched Consultant Panel review 3/28/2018. No change to policy statement. Medical Director review. (lpr)

7/27/18  Reference added. No change to policy statement. (lpr)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.